

CORRESPONDENCE

Thrombotic Thrombocytopenia after Ad26.COVS Vaccination

TO THE EDITOR: Thrombosis and thrombocytopenia have been reported after vaccination with the ChAdOx1 nCoV-19 vaccine (Oxford–AstraZeneca), a recombinant chimpanzee adenoviral vector encoding the spike glycoprotein of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).^{1,2} To date, such reactions have not been associated with other vaccines against coronavirus 2019 (Covid-19). We describe a case of extensive thrombosis associated with severe thrombocytopenia and disseminated intravascular coagulation that resembled autoimmune heparin-induced thrombocytopenia³ in a patient who had received the Ad26.COVS vaccine (Johnson & Johnson/Janssen), a recombinant adenovirus serotype 26 vector encoding the SARS-CoV-2 spike glycoprotein.

A 48-year-old White woman with an unremarkable medical history presented to the emergency department with a 3-day history of malaise and abdominal pain. The initial evaluation at another hospital showed mild anemia and severe thrombocytopenia (platelet count, 13,000 per cubic millimeter [reference range, 150,000 to 400,000]). A peripheral-blood smear confirmed a marked reduction in the platelet count with occasional schistocytes. Additional studies showed a low fibrinogen level (89 mg per deciliter [reference range, 220 to 397]), a prolonged activated partial thromboplastin time (41 seconds [reference range, 25 to 37]), and a marked elevation in the D-dimer level (117.5 mg per liter [reference value, <0.5]), indicating a disseminated intravascular coagulation–like state. (A complete listing of the patient's laboratory values is provided in the Supplementary Appendix, available with the full text of this letter at NEJM.org.) Computed tomographic (CT) imaging of the abdomen and pelvis showed extensive splanchnic-vein thrombosis.

The patient was transferred to our institution. SARS-CoV-2 RNA was not detected on reverse-transcriptase–polymerase-chain-reaction assay of a sample obtained with a nasopharyngeal swab. Head CT that was performed after a report of

new-onset headache showed cerebral venous sinus thrombosis involving the right transverse and straight sinuses. The administration of unfractionated heparin was initiated, but despite this treatment, the patient had progressive thrombosis with hemorrhagic stroke evident on magnetic resonance imaging and magnetic resonance venography of the brain. Repeat CT angiography showed new thrombus involving the right hepatic and splenic veins.

On further inquiry, it was noted that the patient had received the Ad26.COVS vaccine 14 days before symptom onset. The screening test for antibodies against platelet factor 4 (PF4)–heparin by latex-enhanced immunoassay was negative. However, the result of enzyme-linked immunosorbent assay for antibodies against PF4–polyanion was strongly positive (2.550 optical-density units [upper limit of normal range, ≤ 0.399). Heparin was switched to argatroban. She also received intravenous immune globulin at a dose of 1 g per kilogram of ideal body weight (as calculated according to the actual weight [112 kg] and height [168 cm] of the patient) for 2 days. This treatment was followed by an increase in the platelet count from 30,000 to 145,000 during a 5-day period. The patient remained critically ill at the time of this report.

In a recent study, Greinacher and colleagues¹ (one of whom, Theodore Warkentin, provided valuable advice regarding this patient) found that vaccine-induced immune thrombotic thrombocytopenia was associated with IgG antibodies that recognize PF4 and activate platelets through their Fc γ receptors. Inhibition of platelet activation by intravenous immune globulin paralleled its efficacy in the treatment of autoimmune heparin-induced thrombocytopenia.⁴

We note with interest that during the clinical evaluation of the Ad26.COVS vaccine, a 25-year-old man was found to have symptomatic transverse sinus thrombosis beginning 19 days after vaccination. Although the case investigation and expert opinion deemed this event to be unrelated to the vaccine,⁵ this finding may require reevalu-

ation in light of our patient's clinical course. Unlike the Pfizer–BioNTech and Moderna vaccines, which are messenger RNA–based, the ChAdOx1 nCov-19 and Ad26.COV2.S vaccines are nonreplicating adenovirus vector–based DNA vaccines. Our case suggests that the rare occurrence of vaccine-induced immune thrombotic thrombocytopenia could be related to adenoviral vector vaccines.

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Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

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